

Appl. No. 10/560,509
Amdt. Dated January 25, 2010
Reply to Office Action of August 25, 2009

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Revised claims are submitted, wherein the subject matter of claim 1 has been limited to a 'radioactive imaging moiety'. Basis can be found at page 6 lines 17 to 19 of the specification. Accordingly, the subject matter of previous claims 7, 9 and 10 has been cognated into revised claim 1. Claim 1 has also been limited to the specific inhibitors of previous claim 13, and a K_i value of less than 500 nM. Basis for the latter amendment can be found at page 5 lines 9 to 10 of the specification. Claim 26 has been amended to incorporate the features of claim 29.

Listing of Claims:

1. (Currently amended) An imaging agent which comprises a synthetic caspase-3 inhibitor labelled with an imaging moiety, wherein ~~the caspase-3 inhibitor has a K_i for caspase-3 of less than 2000 nM, and wherein following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety can be detected either externally in a non invasive manner or via use of detectors designed for use *in vivo*~~ following administration of said labelled caspase-3 inhibitor to the mammalian body *in vivo*, the imaging moiety is suitable for imaging using SPECT or PET and said imaging moiety is chosen from:
 - (a) a radioactive metal ion chosen from ^{99m}Tc , ^{111}In , ^{64}Cu , ^{67}Cu , ^{67}Ga or ^{68}Ga ;
 - (b) a gamma-emitting radioactive halogen which is ^{123}I ;
 - (c) a positron-emitting radioactive non-metal chosen from ^{18}F , ^{11}C , ^{124}I or ^{13}N ;wherein the synthetic caspase-3 inhibitor has a K_i for caspase-3 of less than 500 nM and comprises one or more of the caspase-3 inhibitors defined in (i) to (iii):

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(i) a tetrapeptide derivative of Formula III



where Z^1 is a metabolism inhibiting group attached to the N-terminus of the tetrapeptide;

Xaa1 and Xaa2 are independently any amino acid;

X^1 is an $-R^1$ or $-\text{CH}_2\text{OR}^2$ group attached to the carboxy terminus of the tetrapeptide;

where R^1 is H, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{Cl}$, C_{1-5} alkyl, C_{1-5} alkoxy or $-(\text{CH}_2)_q\text{Ar}^1$, where q is an integer of value 1 to 6 and Ar^1 is C_{6-12} aryl, C_{5-12} alkyl-aryl, C_{5-12} fluoro-substituted aryl, or C_{3-12} heteroaryl;

R^2 is C_{1-5} alkyl, C_{1-10} acyl or Ar^1 ;

(ii) a 2-oxindole sulfonamide;

(iii) a dipeptide of Formula VI:



where the $-\text{CH}_2\text{SR}^1$ group is attached to the carboxy terminus of the dipeptides, and Z^1 and R^1 are as defined for Formula (III).

2. (Cancelled)

3. (Previously presented) The imaging agent of Claim 1, where the synthetic caspase-3 inhibitor has a molecular weight of 150 to 3000 Daltons.

4.- 13 (Cancelled).

14. (Previously presented) The imaging agent of Claim 1, where the synthetic caspase-3 inhibitor is selective for caspase-3 over caspase-1, by a factor of at least 50.

15. (Cancelled) .

16. (Cancelled).

17. (Currently amended) A radiopharmaceutical composition which comprises the imaging agent of Claim 1 ~~wherein the imaging moiety is radioactive~~, together with a biocompatible carrier, in a form suitable for mammalian administration.

18. (Original) The radiopharmaceutical composition of claim 17, where the imaging moiety comprises a positron-emitting radioactive non-metal or a gamma-emitting radioactive halogen.

19. – 25. (Cancelled).

26. (Currently amended) A kit for the preparation of the radiopharmaceutical composition of Claim 18, which comprises a precursor, said precursor being a non-radioactive derivative of a caspase-3 inhibitor, wherein the caspase-3 inhibitor is as defined in claim 1 ~~has a K_i for caspase 3 of less than 2000 nM~~, wherein said non-radioactive derivative is capable of reaction with a source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen to give the desired radiopharmaceutical, and said non-radioactive derivative is chosen from:

- a an organometallic derivative such as a trialkylstannane or a trialkylsilane;
- b a derivative containing an alkyl halide, alkyl tosylate or alkyl mesylate for nucleophilic substitution;
- c a derivative containing an aromatic ring activated towards nucleophilic or electrophilic substitution;
- d a derivative containing a functional group which undergoes facile alkylation;
- e a derivative which alkylates thiol-containing compounds to give a thioether-containing product.

27. (Original) The kit of claim 26 where the precursor is in sterile, apyrogenic form.

28. (Previously presented) The kit of Claim 26, where the source of the positron-emitting radioactive non-metal or gamma-emitting radioactive halogen is chosen from:

- a halide ion or F⁺ or I⁺; or
- b an alkylating agent chosen from an alkyl or fluoroalkyl halide, tosylate, triflate or mesylate;

29. (Cancelled).

30. (Previously presented) The kit of claim 26, where the precursor is bound to a solid phase.

31. (Currently amended) ~~Use of the imaging agent of Claim 1 in a A method of diagnosis of a caspase-3 implicated disease state of the mammalian body, wherein said mammal is previously administered with the pharmaceutical composition which comprises the imaging agent of Claim 1 together with a biocompatible carrier, in a form suitable for mammalian administration, or the radiopharmaceutical composition of claim 17 which comprises the imaging agent of Claim 1 wherein the imaging moiety is radioactive, together with a biocompatible carrier, in a form suitable for mammalian administration imaging said mammal using SPECT or PET.~~